

```

# fupl: unbound fraction in plasma

# pKa: compound dissociation constant
# Pow: octanol:water partition coefficient
# Dplw: phospholipid:water distribution coefficient
# alpha: Ratio of Distribution coefficient D of totally charged species and that of the
neurtral form
# KAPPACell2plasma: Ratio of D inside the cell to D in the plasma, as derived from the
different pHs and pKas
# FPpl: protein fraction in plasma - from Gardner 1980

# This predicts the coefficient of tissue to FREE plasma fraction via Schmitt's method (2004):
Predict_Ktissue2plasma <- function(fupl,
  pKa,
  Pow,
  Dplw=NULL,
  alpha=0.001,
  KAPPACell2plasma=1.0,
  FPpl = 75/1000/1.025,
  tissuelist=NULL,
  species="Human",
  Davis.corrected=TRUE)
{

tissue.data[tissue.data$Tissue=="Rest",2:10]<-average.tissue[average.tissue$X==species,2:10]

Ktissue2plasma <- list()
vol <- list()
flow <- list()

# water fraction in plasma:
FWpl <- 1 - FPpl
# protein fraction in interstitium:
FPint <- 0.37 * FPpl
# water fraction in interstitium:
FWint <- FWpl

if (is.null(tissuelist))
{
  tissuelist <- as.list(tissue.data$Tissue)
  names(tissuelist) <- tissue.data$Tissue
}

all.tissues <- rep(FALSE,length(tissue.data$Tissue))
names(all.tissues) <- tissue.data$Tissue

for (this.lumped.tissue in c(names(tissuelist),"Red blood cells","cleanup"))
{
  if (this.lumped.tissue == "cleanup")
  {
    this.lumped.tissue <- "Rest"
    if (!("Rest" %in% names(vol)))
    {
      vol[[this.lumped.tissue]] <- 0
      flow[[this.lumped.tissue]] <- 0
      Ktissue2plasma[[this.lumped.tissue]] <- 0
    }
  }
}

```

```

        }
        these.lumped.tissues <- tissue.data$Tissue[!all.tissues]
    } else {
        if (this.lumped.tissue == "Red blood cells")
        {
            vol[[this.lumped.tissue]] <- NA
            flow[[this.lumped.tissue]] <- NA
            if (!all.tissues["Red blood cells"])
            {
                these.lumped.tissues <- "Red blood cells"
                Ktissue2plasma[[this.lumped.tissue]] <- 0
            } else these.lumped.tissues <- NULL
        } else {
            vol[[this.lumped.tissue]] <- 0
            flow[[this.lumped.tissue]] <- 0
            Ktissue2plasma[[this.lumped.tissue]] <- 0
            these.lumped.tissues <- tissuelist[[this.lumped.tissue]]
        }
    }
    for (this.tissue in these.lumped.tissues)
    {
        if (!(this.tissue %in% tissue.data$Tissue))
            stop(paste(this.tissue,"not in list",paste(tissue.data$Tissue)))
        if (all.tissues[[this.tissue]] & this.tissue != "Rest")
            stop(paste(this.tissue,"assigned to multiple lumped tissues"))

        all.tissues[[this.tissue]] <- TRUE
        this.row <- tissue.data$Tissue==this.tissue

        vol[[this.lumped.tissue]] <- vol[[this.lumped.tissue]] +
        as.numeric(tissue.data[this.row,paste(species,"Vol (L/kg)",sep=" ")])
        flow[[this.lumped.tissue]] <- flow[[this.lumped.tissue]] +
        as.numeric(tissue.data[this.row,paste(species,"Flow (mL/min/kg)",sep=" ")])

        Fcell <- as.numeric(tissue.data[this.row,"Fcell"])
        # interstitial volume fraction:
        Fint <- as.numeric(tissue.data[this.row,"Fint"])
        if (is.na(Fint)) Fint <- 0

        # water volume fraction:
        FW <- Fcell * as.numeric(tissue.data[this.row,"FWc"])
        # neutral lipid volume fraction:
        Fn_L <- Fcell * as.numeric(tissue.data[this.row,"FLc"]) *
        as.numeric(tissue.data[this.row,"Fn_Lc"])
        if (is.na(Fn_L)) Fn_L <- 0
        # neutral phospholipid volume fraction:
        Fn_PL <- Fcell * as.numeric(tissue.data[this.row,"FLc"]) *
        as.numeric(tissue.data[this.row,"Fn_PLC"])
        if (is.na(Fn_PL)) Fn_PL <- 0
        # acidic phospholipid volume fraction:
        Fa_PL <- Fcell * as.numeric(tissue.data[this.row,"FLc"]) *
        as.numeric(tissue.data[this.row,"Fa_PLC"])
        if (is.na(Fa_PL)) Fa_PL <- 0
        # protein volume fraction:
        FP <- Fcell * as.numeric(tissue.data[this.row,"FPc"])
    }
}

```

```

# print(paste(this.tissue,"Fcell",Fcell,"Fint",Fint,"FW",FW,"Fn_L",Fn_L,"Fn_PL",Fn_PL,"Fa_PL",Fa
_PL,"FP",FP))

# tissue pH
pH <- as.numeric(tissue.data[this.row,"pH"])

# # plasma:protein partition coefficient
KPpl = 1/FPpl*(1/fopl-FWpl)

# neutral phospholipid:water partition coefficient:
if (is.null(Dplw))
{
  Kn_PL <- Pow
} else {
  Kn_PL <- Dplw
}

# Octanol:water distribution coefficient:
if (pH <= 7)
{
  Dow <- Pow*((1 - alpha)/(1+10^(pH-pKa)) + alpha)
} else {
  Dow <- Pow*((1-alpha)/(1+10^(pKa-pH)) + alpha)
}

# neutral lipid:water partition coefficient
Kn_L <- Dow

# protein:water partition coefficient:
KP <- 0.163 + 0.0221*Kn_PL

# acidic phospholipid:water partition coefficient:
if (pH <= 7)
{
  Ka_PL <- Kn_PL * (1/(1+10^(pH-pKa)) + 20*(1 - 1/(1+10^(pH-pKa))))
} else {
  Ka_PL <- Kn_PL * (1/(1+10^(pKa - pH)) + 0.05*(1 - 1/(1 + 10^(pKa -
pH)))))

}

# unbound fraction in interstitium:
fuint <- 1/(FWint + FPint/FPpl*(1/fopl - FWpl))

# unbound fraction in cellular space:
fucell <- 1/(FW + Kn_L*Fn_L+Kn_PL*Fn_PL+Ka_PL*Fa_PL+KP*FP)

this.PC <- ((Fint/fuint + KAPPACell2plasma*Fcell/fucell))*fopl

if (Davis.corrected)
{
  if (this.tissue=="Adipose") this.PC <- 0.46222*this.PC
  if (this.tissue=="Bone") this.PC <- this.PC + 0.55791
  if (this.tissue=="Gut") this.PC <- 0.49591*this.PC + 0.35056
  if (this.tissue=="Kidney") this.PC <- 0.63812*this.PC + 0.61411
  if (this.tissue=="Liver") this.PC <- this.PC + 0.37409
}

```

```

if (this.tissue=="Lung") this.PC <- this.PC + 0.52108
if (this.tissue=="Muscle") this.PC <- this.PC + 0.22873
if (this.tissue=="Skin") this.PC <- 0.42136*this.PC
if (this.tissue=="Testis") this.PC <- this.PC + 0.59415
if (this.tissue=="Thymus") this.PC <- this.PC + 0.8962
}

this.PC <- this.PC/fupl

if (this.tissue == "Red blood cells") Ktissue2plasma[[this.lumped.tissue]] <-
this.PC
else Ktissue2plasma[[this.lumped.tissue]] <- Ktissue2plasma[[this.lumped.tissue]] +
vol[[this.lumped.tissue]]*this.PC
}
if (this.lumped.tissue != "Red blood cells") Ktissue2plasma[[this.lumped.tissue]] <-
Ktissue2plasma[[this.lumped.tissue]]/vol[[this.lumped.tissue]]
}

return(list(Ktissue2plasma=Ktissue2plasma,vol=vol,flow=flow))
}

```